

What is the relationship between whole grain intake and cardiovascular disease?

Conclusion

A moderate body of evidence from large prospective cohort studies shows that whole grain intake, which includes cereal fiber, protects against cardiovascular disease.

Grade: Moderate

Overall strength of the available supporting evidence: Strong; Moderate; Limited; Expert Opinion Only; Grade not assignable For additional information regarding how to interpret grades [click here](#).

Evidence Summary Overview

Seven articles (one systematic review, two meta-analyses, one randomized controlled trial (RCT) and three prospective cohorts that were published after the systematic reviews) met the inclusion criteria and were reviewed to determine the effect of whole grain consumption on cardiovascular disease. Of the seven articles, four were of positive quality (Flint, 2009; Kelly, 2007; Mellen, 2008; Nettleton, 2008) and three were of neutral quality (Brownlee, 2010; DeMoura, 2009; Djousse, 2007).

The importance of agreed upon definitions for whole grains was noted in the DeMoura et al, (2009) review. Their initial inclusion criteria required studies to explicitly state the use of the Food and Drug Administration (FDA) definition for whole grains, 51% of weight being whole grains, to be eligible for review. Using this standard, only two RCTs, one prospective, cohort study and one cross-sectional study were identified for review. A second, broader set of inclusion criteria used a minimum level of 25% of whole grain by dry weight to assign values for whole grains and added bran or germ along with whole grains. It is important to note that RCTs conducted with individual whole grains, such as whole grain barley, oats, and rye, were included in the broader definition group, for which a total of 29 studies (15 intervention and 14 observational) were deemed eligible for review. All of the observational studies found a protective association between whole grain intake and cardiovascular disease (CVD) risk. Six RCTs found a beneficial effect of oats on CVD outcomes; five showed no effect. The positive studies had a longer intervention periods (six to eight weeks vs. three weeks). Four RCTs with barley showed reduction in plasma total cholesterol (TC) (20-15%) and LDL cholesterol (LDL-C) (21%) levels across diverse populations. The authors concluded that, for the restricted assessment, while two observational studies found a significant reduction in CVD-related surrogate end-points, there were not supporting intervention studies, thus there was not sufficient evidence to support a whole grain health claim for CVD risk reduction. Using the broader definition, the authors concluded that the evidence supported a whole-grain health claim for reduced risk of CVD.

Two meta-analyses of whole grains and CVD found a protective effect of whole grains on CVD. Kelly et al, (2007), a systematic review and meta-analysis of nine RCTs (eight oat, one rye), reported a significantly lower TC and LDL-C with higher whole grain intake. Mellen et al, (2008), a meta-analysis of seven prospective cohort studies, conducted pooled analysis and found that greater whole grain intake (pooled average 2.5 servings per day vs. 0.2 servings per day) was associated with a 21% lower risk of CVD events (OR 0.79; 95% CI: 0.73-0.85). Similar estimates were noted for other CVD outcomes, including incident coronary heart disease (CHD), stroke and fatality. The authors' concluded that evidence from prospective cohort studies consistently showed an inverse association between dietary whole grains and incident CVD.

One RCT (Brownlee et al, 2010) examined markers of cardiovascular risk in a large (N=266) intervention study with high risk (BMI>25kg/m²) subjects. Subjects who routinely consumed few whole grain products were randomized to control group, 60g whole grains per day for eight weeks, or 60g per day for eight weeks then 120g per day for eight more weeks. Cardiovascular disease biomarkers were measured at baseline, eight and 16 weeks. There were no differences in BMI, percentage body fat, waist circumference, fasting plasma lipid profile, glucose or insulin.

Three prospective cohort studies examined whole grain intake and cardiovascular outcomes. Flint et al, (2009), 18-year follow-up of the Health Professional's Study, quantified whole grain intake in grams and found that whole grain intake was inversely associated with risk of hypertension (HTN) (RR=0.81; P<0.0001). The RR for total bran was 0.85 (P=0.002). The authors concluded that there was an independent inverse association between whole grain intake and incident HTN in men. Bran, an integral component of whole grains, may play an important role in this association.

Djousse and Graziano, (2007) concluded that there was an inverse association between whole grain breakfast cereal consumption and the risk of heart failure (HF). Similarly, Nettleton et al, (2008) concluded that in their large population-based cohort of the

ARIC study (N=14,153 African-American and white adults) whole grain intake was associated with lower HF risk. The multivariate-adjusted heart failure risk for whole grain intake was 0.93 (P<0.05) for each one serving per day increase in whole grain consumption.

Evidence Summary Paragraphs

Systematic Reviews/Meta-analyses

De Moura et al, 2009 (neutral quality) a systematic review, conducted in the United States, evaluated the strength of scientific evidence in support of health claims for risk reduction of cardiovascular disease (CVD) when applying the FDA whole grain definition vs. applying a broader whole grain definition that is more commonly used in scientific studies. The restricted analysis was limited to studies that explicitly defined grains according to the FDA definition of whole grains, "intact, ground, cracked or flaked fruit of the grains whose principal components, the starchy endosperm, germ and bran are present in the same relative proportions as they exist in intact grain." Four studies (two RCTs, one prospective cohort, one cross-sectional study) met the criteria and were included in the restricted analysis. The two RCTs did not find significant differences for surrogate CVD endpoints such as TC, LDL-C and blood pressure (BP). The prospective cohort study reported a reduced relative risk of coronary heart disease (CHD) in men when comparing the highest to the lowest quintiles of whole grain intake (P for trend=0.01). The cross-sectional study observed a decrease in total cholesterol of 0.16mmol/L when comparing the extreme quintiles of whole grain intake (P for trend=0.02). The expanded analysis included a broader definition that added bran or germ along with whole grains, as well as studies that were conducted with individual whole oat and rye grains. A total of 29 studies (15 intervention and 14 observational) were included. All of the observational studies found a protective association between whole grain intake and CVD risk. Six RCTs found a beneficial effect of oats on CVD outcomes; four found a significant positive effect (P<0.05), and one showed no effect. The positive studies had a longer intervention periods (six to eight weeks vs. three weeks). Four RCTs with barley showed reduction in plasma TC (20-15%) and LDL-C (21%) levels across diverse populations. The authors concluded that, for the restricted analysis, while two observational studies found a significant reduction in CVD-related surrogate endpoints, there were not supporting intervention studies, thus there was not sufficient evidence to support a whole grain health claim for CVD risk reduction. Using the broader definition, the authors concluded that the evidence supported a whole-grain health claim for reduced risk of CVD.

Kelly SAM et al, 2007 (positive quality) a Cochrane systematic review, conducted in the United Kingdom, examined RCTs that studied the effect of whole-grain consumption on CHD risk factors, morbidity and mortality, in subjects with existing CHD risk factors or previously diagnosed with CHD. Ten trials met the criteria for review, including minimum study duration of four weeks. Nine of the 10 trials, reported the effect of whole-grain foods or diets on risk factors for CHD; no studies examining the effect of whole-grains on CHD events or mortality were found. Eight studies examined the effect of an oat intervention; seven of them reported lower TC and LDL-C compared to the controls. Meta-analysis of the eight studies found a lower total and LDL-C with oatmeal foods (-0.20mmol/L, 95% CI: -0.31 to -0.10, P=0.0001) and (0.18mmol/L, 95% CI: -0.28 to -0.09, P<0.0001), respectively. Pooling the rye study with the other data for oatmeal did not change the results. Heterogeneity was not found in the pooled analyses for TC, LDL-C, HDL cholesterol and triglycerides (TG). Overall, the authors concluded that, despite the consistency of effects seen in whole grain oat trials, there was insufficient evidence to make any conclusions about whole grain diets other than oatmeal. They also indicated that many of the trials identified were short term, of poor quality and had insufficient power. They identified the need for well-designed, adequately powered, longer term RCTs on whole grain foods and diets other than oats.

Mellen P et al, 2008 (positive quality) a meta-analysis, conducted in the United States, quantified observational evidence on whole grain intake and clinical cardiovascular events. Seven prospective cohort studies with quantitative measures of dietary whole grains and clinical cardiovascular outcomes were identified for pooled analysis. Six studies provided information for demographic adjusted analyses and seven for risk-factor-adjusted analyses. Based on event estimates adjusted for cardiovascular risk factors, greater whole grain intake (pooled average 2.5 servings per day vs. 0.2 servings per day) was associated with a 21% lower risk of CVD events (OR 0.79; 95% CI: 0.73-0.85). The findings were similar when analyses were restricted to studies that provided gender-specific results for men (OR: 0.82, 95% CI: 0.73-0.92) and women (OR: 0.79, 95% CI: 0.68-0.91). Similar estimates were noted for other CVD outcomes, including incident CHD, stroke and fatal. The authors' concluded that evidence from prospective cohort studies consistently showed an inverse association between dietary whole grains and incident cardiovascular disease.

Primary Studies

Brownlee I et al, 2010 (neutral quality) an RCT, conducted in the United Kingdom, investigated the effect of substituting whole grain for refined grains on CVD risk markers. Subjects (N=266; BMI>25kg/m²) who routinely consumed few whole grain products were randomized to consume 60g whole grains per day for eight weeks or 60g whole grains per day for eight weeks and then 120g whole grains per day for eight more weeks. Markers of CVD risk (BMI, percent body fat, waist circumference; fasting plasma lipid profile, glucose and insulin) were measured at baseline, eight and 16 weeks. A random intercepts model with time and whole grain intake factors was used to assess differences between the control and the average of the two intervention groups. Self-reported whole grain intake was significantly increased in both intervention groups. No significant differences in CVD risk markers were found between the control and the averaged intervention groups between groups.


Djousse L and Graziano J, 2007 (neutral quality) a prospective cohort study, conducted in the United States, evaluated the



association between breakfast cereal intake and incident heart failure (HF) in a cohort of the Physicians' Health Study (N=21,376 men, aged 40-86 years). Cereal consumption was estimated using a semi-quantitative food frequency questionnaire (FFQ). Incident HF was determined from annual follow-up questionnaires and validated using Framingham criteria. Cox regression models were used to estimate adjusted relative risk of HF across categories of cereal intake. During an average follow-up of 19.6 years, 1,018 incident cases of HF occurred. The multivariate adjusted RR for the extreme quintiles of average weekly whole grain cereal consumption (zero servings per week to at least seven or more servings per week was 0.72 (95% CI: 0.59-0.88); P<0.001. The association for refined cereals was not significant (NS) (P=0.70 for trend). The authors concluded that there was an inverse association between whole grain breakfast cereal consumption and the risk of heart failure.


Flint A et al, 2009 (positive quality) a prospective cohort study, conducted in the United States, examined the association between whole grain intake (grams per day) and risk of incident HTN in a cohort from the Health Professionals Follow-Up Study (N=31,684 males, baseline age 40-75 years). Whole grain intake was measured at baseline and with administration of each follow-up food frequency questionnaire. A total of 9,227 cases of incident hypertension were reported over the 18 years of follow-up. In multivariate-adjusted analyses, comparing the extreme quintiles of consumption, whole grain intake was inversely associated with risk of HTN, (RR=0.81 (95% CI: 0.75-0.87, P<0.0001). The RR for total bran was 0.85 (95% CI: 0.78, 0.92, P=0.002). The authors concluded that there was an independent inverse association between whole grain intake and incident HTN in men. Bran may play an important role in this association.



Nettleton J et al, 2008 (positive quality) a prospective cohort study, conducted in the United States, studied the relationships between incident heart failure (HF) (death or hospitalization) and consumption of seven food categories (whole grains, fruits and vegetables, fish, nuts, high-fat dairy, eggs, red meat). The subjects were a cohort of the Atherosclerosis Risk in Communities (ARIC) study (N=14,153 African-American and white adults, age 45 to 64 years). Dietary intake was assessed using a validated 66-item FFQ. During a mean follow-up period of 13 years, 1,140 cases of incident HF were identified. Heart failure hazard ratios (HR) were calculated on a one serving per day difference in each food group intake. The multivariate-adjusted HF risk for whole grain intake was 0.93 (95% CI: 0.87, 0.99; P<0.05) for each one serving per day difference in consumption. This association remained significant independent of intakes of the other food categories analyzed. The authors concluded that in their large, population-based sample of African-American and white adults whole grain intake was associated with lower HF risk.


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Author, Year, Study Design, Class, Rating	Participants, Duration and Location	Description of Study Design	Outcomes	Whole Grain Definition
Brownlee IA, Moore C et al, 2010 Study Design: Randomized controlled trial Class: A Rating: 	N=266 participants. Age: 18-65 years. BMI>25kg/m ² . Consuming <30g whole grain per day.	Examined effect of substituting whole grain for refined grains on CVD risk markers using random intercepts model Interventions: Control (no dietary Δ) Int 1: 60g whole grain per day x 16 weeks Int 2: 60g whole grain per day x eight weeks, then 120g whole grain per day for eight weeks	<i>Dropout rates:</i> Int 1=19% Int 2=23% Control=6% Int 1 and 2 outcome measures were averaged and then compared to controls. There were NS differences in any markers of CVD risk between the combined intervention groups and the control.	Selected whole grain foods were provided to free-living subjects.

		Measures taken at zero, eight and 16 weeks. Whole grain foods were provided; intake data was self-reported on EPIC FFQ.		
<p>De Moura FF, Lewis KD et al, 2009</p> <p>Study Design: Meta-analysis or Systematic Review</p> <p>Class: M</p> <p>Rating: </p>	<p>Restricted analysis: N=4 studies; two RCT and two observational.</p> <p>Expanded analysis: N=29 studies; 15 RCT and 14 observational.</p> <p>Location: Most of the studies were conducted in the US (one each in China, England, Germany Iran, Japan and Sweden).</p>	<p>Evaluated the strength of scientific evidence in support of claims for CVD risk reduction using two whole grain definitions; the FDA definition vs. a broader definition commonly used in scientific studies.</p> <p>Lit search: MEDLINE for primary studies published through Feb 2008.</p> <p>English language only.</p> <p>Study quality was not assessed.</p>	<p>Six RCTs found a beneficial effect of oats on CVD outcomes; four found a significant positive effect ($P<0.05$) and one showed no effect. The positive studies had a longer intervention periods (six to eight weeks vs. three weeks). Four RCTs with barley showed reduction in plasma TC (20-15%) and LDL-C (21%) levels across diverse populations.</p> <p>The estimates and CIs were not reported.</p> <p>All of the observational studies found a protective association between whole grain intake and CVD risk.</p>	<p>FDA: Whole grains consist of the intact, ground, cracked or flaked fruit of the grains whose principal components-the starchy endosperm, germ and bran-are present in the same relative proportions as they exist in the intact grain.</p> <p>Expanded: Added bran or germ along with whole grains, as well as RCTs that were conducted with individual whole grain oats or rye.</p>
<p>Djousse L and Gaziano JM, 2007</p> <p>Study Design: Prospective Cohort Study</p> <p>Class: B</p> <p>Rating: </p>	<p>N=21,376 male subjects (Cohort of Physician's Health Study I).</p> <p>Baseline age: 40-86 years.</p> <p>Duration: 19.6 years of follow-up.</p> <p>Location: United States.</p>	<p>Examined the relationship between consumption of breakfast cereals and risk of heart failure (HF).</p> <p>Used a semi-quantitative FFQ to collect intake data. Cereal consumption obtained at baseline, 18 weeks and 24, 48, 72, 96 and 120</p>	<p>1,018 incident cases of heart failure occurred.</p> <p>Consumption of at least seven servings of whole grain breakfast cereals per week was associated with a reduced incidence of HF: RR=0.72 (95% CI: 0.59-0.88; $P<0.001$).</p>	<p>Used algorithm developed by Jacobs et al, AJCN 1998 to classify foods as whole or refined grain.</p> <p>One serving=One cup of cold ready-to-eat cereal.</p> <p>Brand of cereals consumed</p>

		<p>months after randomization.</p> <p>Incident HF ascertained through annual follow-up questionnaires and validated using Framingham criteria.</p>		<p>resulted in classification of whole grain or refined grain.</p> <p>Breakfast cereals containing at least 25% whole grain or bran by weight were classified as whole grain.</p>
<p>Flint AJ, Hu FB et al, 2009</p> <p>Study Design: Prospective Cohort Study</p> <p>Class: B</p> <p>Rating: </p>	<p>N=31,684 males, (Cohort of the Health Professional's Follow-Up Study).</p> <p>Baseline age: 40-75 years.</p> <p>Follow up duration: 18 years.</p> <p>Location: United States.</p>	<p>Examined the association between whole grain intake (grams per day) and risk of incident HTN.</p> <p>Semi-quantitative FFQ used to obtain whole grain intake data.</p> <p>This study employed a new food composition database, which allowed estimation of whole-grain intake in grams per day, is described in detail elsewhere</p> <p>Incident HTN was obtained by self-report on bi-ennial questionnaires. This approach was validated in this cohort.</p>	<p>9,227 cases of incident HTN were reported</p> <p>Multivariate-adjusted RR for the highest quintile of whole grain consumption (46.0g per day)=0.81 (95% CI: 0.75-0.87, P<0.0001).</p> <p>The RR for the highest quintile of total bran (12.0g per day)=0.85 (95% CI: 0.78, 0.92, P=0.002).</p>	<p>Whole grains were considered by definition to contain the expected proportion of bran, endosperm and germ for the specific grain type.</p> <p>Whole grains, bran and germ were calculated by determining the whole-grain content of each grain food according to the dry weight of its whole-grain ingredients.</p> <p>Nutrient profiles of the various grain foods were derived by using composite recipes, US Department of Agriculture nutrient data, and product labels, whereas cookbooks were used to estimate contents of home-prepared</p>


				bakery items.
<p>Kelly et al 2007 (Cochrane)</p> <p>Study Design: Meta-analysis; systematic review (Cochrane)</p> <p>Class: M</p> <p>Rating: </p>	<p>10 RCT met the inclusion criteria.</p> <p>Duration: Four-week minimum.</p> <p>Subjects included adults with existing CHD or at least one CHD risk factor.</p> <p>Location: Nine studies were conducted in the United States and one in Finland.</p> <p>Literature search date ranges spanned from 1966 to 2005 and varied by database. No language restrictions were applied.</p>	<p>Examined the effect of whole grain food consumption on CHD risk factors, morbidity and mortality.</p> <p>Eight trials studied oat foods.</p> <p>One compared whole meal rye to refined wheat bread.</p> <p>One compared a whole grain diet to a refined grain diet.</p>	<p>Seven of eight parallel oat studies reported lower total cholesterol in the whole grain groups compared to controls.</p> <p>Meta-analysis (eight oat studies) found an effect on total cholesterol in the whole grain group compared to the control Group; direction favored lower total cholesterol on whole grain diets; weighted mean difference= -0.19mmol/L 95% CI -0.30 to -0.08 P=0.0005</p> <p>Addition of the rye cross-over study weighted mean difference= -0.20, 95% CI -0.31 to -0.10, P=0.0001.</p> <p>Sensitivity analysis without the Reynolds study: -0.23 95% CI -0.33 to -0.12.</p> <p>Additional, removal of the Keenan study (small number of subjects) weighted mean difference: -0.22mmol/L, 95% CI -0.33 to -0.10.</p> <p>Sensitivity analysis: Heterogeneity was not found in the pooled analysis for total, LDL-C or HDL-C and TG.</p> <p>All 10 studies were graded quality level "C" based on the Cochrane criteria. Since all trials received the same quality rating, sensitivity analysis on the basis of quality was not performed.</p>	<p>Included foods based on milled whole grains, such as whole meal or oatmeal, where the components of the endosperm, bran and germ had not been removed.</p>
<p>Mellen PB, Walsh TF & Herrington DM 2008</p> <p>Study Design: Meta-analysis</p> <p>Class: M</p> <p>Rating: </p>	<p>Pooled data from seven prospective cohort studies.</p> <p>Total N for pooled analysis=149,000 male and female subjects.</p> <p>Age: 35 to 98 years.</p> <p>Follow up duration: Six to 15 years.</p> <p>Location: Six studies from the United States, one from Norway.</p>	<p>Evaluated the association between whole grain intake and clinical CVD events using the following criteria:</p> <ol style="list-style-type: none"> 1. The studies used self-reported quantitative measures of whole grain intake (e.g., servings per day) 2. CVD events 	<p>Mantel-Haentzel test for heterogeneity found no evidence of significant heterogeneity, so fixed-effects models were used.</p> <p>Incident CVD:</p> <p>Demographic-adjusted CVD estimates (OR): 0.63; 95% CI: 0.58-0.68.</p> <p>Risk-factor-adjusted CVD estimates: 0.79; 95% CI: 0.73-0.85.</p> <p>Sex-specific CVD</p>	<p>Whole grain definition not stated.</p> <p>Included only studies that reported a quantitative whole-grain intake in servings per day.</p>

		<p>were ascertained prospectively</p> <p>3. Data provided was adequate to generate adjusted event rates.</p> <p>Literature search in MEDLINE; date range=1966 to April 2006.</p>	<p>estimate: Men: 0.82; 95% CI: 0.73-0.92; Women: 0.79; 95%CI: 0.68-0.91.</p> <p>Fatal CVD end-points: 0.78; 95% CI: 0.70-0.88.</p> <p>Incident CHD end-points: 0.76; 95% CI: 0.69-0.83.</p> <p>Incident stroke end-points: 0.83; 95% CI: 0.68-1.02.</p> <p>Funnel plots and Egger test used to evaluate publication bias.</p>	
<p>Nettleton JA et al 2008</p> <p>Study Design: prospective cohort study</p> <p>Class: B</p> <p>Rating: </p>	<p>N=14,153 African-American and white adults (Cohort of the Atherosclerosis Risk in Communities study).</p> <p>Age: 45 to 64 years.</p> <p>Follow up duration: 13 years.</p> <p>Location: United States.</p>	<p>Used a 66-item FFQ to examine the association between incident heart failure (HF) (death or hospitalization) and consumption of seven food categories (whole grains, fruits, vegetables, fish, nuts, high-fat dairy, eggs, red meat).</p> <p>Hazard ratios for HF were calculated on a one serving per day difference in each food group intake.</p> <p>Incident HF defined as first HF hospitalization (428, ICD-9). HF fatality based on any death certificate with an HF code (428, ICD-9 and I50, ICD-10).</p>	<p>1,140 cases of incident HF identified.</p> <p>Multivariate-adjusted HF risk for each one serving per day increase in whole-grain intake=0.93 (95% CI: 0.87, 0.99; P<0.05).</p>	<p>Whole grain and what constituted one serving were not defined in the manuscript.</p> <p>Citation for validated FFQ was Willett WC et al, <i>Am J Epi</i>, 1985</p>


Research Design and Implementation Rating Summary


For a summary of the Research Design and Implementation Rating results, [click here](#).

Worksheets


 [Brownlee IA, Moore C, Chatfield M, Richardson DP, Ashby P, Kuznesof SA, Jebb SA, Seal CJ. Markers of cardiovascular risk are not changed by increased whole-grain intake: The WHOLEheart study, a randomised, controlled dietary intervention. *Br J Nutr*. 2010 Mar 23: 1-10.](#)


 [De Moura FF, Lewis KD, Falk MC. Applying the FDA definition of whole grains to the evidence for cardiovascular disease health claims. *J Nutr*. 2009 Nov; 139 \(11\): 2,220S-2,226S.](#)

 [Djousse L, Gaziano JM. Breakfast cereals and risk of heart failure in the Physicians Health Study I. *Arch Intern Med*. 2007; 167\(19\): 2,080-2,085.](#)

 [Flint AJ, Hu FB, Glynn RJ, Jensen MK, Franz M, Sampson L, Rimm EB. Whole grains and incident hypertension in men. *Am J Clin Nutr*. 2009 Sep; 90 \(3\): 493-498.](#)

 [Kelly, SAM, Summerbell, CD, Brynes, A, Whittaker, V, Frost, G. Wholegrain cereals for coronary heart disease. *Cochrane Database of Systematic Reviews*. 2, 2007](#)

 [Mellen PB, Walsh TF, Herrington DM. Whole grain intake and cardiovascular disease: A meta-analysis. *Nutr Metab Cardiovasc Dis*. 2008 May;18\(4\):283-90.](#)

 [Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities \(ARIC\) Study. *J Am Diet Assoc*. 2008;108:1881-1887.](#)